UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TD

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/023,483	02/13/98	HEROUX J	2528-2

EXAMINER	
TUNG, J	
ART UNIT	PAPER NUMBER
1656	14

DATE MAILED: 02/28/01

HM12/0228

NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON VA 22201

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/023,483	Applicant(s) Heroux et al.
	Examiner Joyce Tung	Group Art Unit 1656

☒ Responsive to communication(s) filed on *9/8/00* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-40* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The request filed on 12/11/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/023,483 is acceptable and a CPA has been established. An action on the CPA follows.

2. Regarding the rejection of claims 1-3, 6-12, 14-25, 28-32 and 34-37 under 35 U.S.C. 103(a) over Hartley in view of Eberle et al., the response argues that Hartley does not disclose detection or quantitation without prior knowledge of specific sequence or detection. This limitation is not in the claim language and Hartley does indicates that the knowledge of a nucleic acid sequence is not required (See column 2, lines 53-58). The response further argues that Hartley does not disclose detection and quantitation of total nucleic acid in a sample. However, Hartley does disclose a process for the amplification of template nucleic acid sequences present in a sample (See column 2, line 54-55) in which the template nucleic acid may be either DNA or RNA (See column 3, lines 15-18) and double stranded or single stranded DNA or single stranded RNA or mRNA (See column 3, lines 22-33) and the method might be desirable in the quantification of the amplification product (See column 6, lines 39-43). The response also argues that Hartley dose not indicate that the amplification will be independent of source/size/sequence, etc. This statement is not understandable. Nevertheless, Hartley indicates that the nucleic acid in a sample will be from any sources (See column 3, lines 6-21) and all kinds of nucleic acid sequences (See column 3, lines 22-33). The response additionally argues that Eberle et al. do not indicate the assay which is independent of nucleic acid size/sequence/complexity, etc, as claimed,

and the method of Eberle for measuring polymerase activity through the use of a well defined template strand nucleic acid sequence. Although the method of Eberle et al. is for determining polymerase activity, polymerase chain reaction is involved in the method of Eberle et al., there is no indication that the template is well defined (See column 3, lines 8-16) and the method of Eberle et al. will be used to detect a promoter sequence (See column 10, lines 59 to column 11, lines 1-9). The promoter sequence is a nucleic acid sequence which indicates that the method of Eberle et al. will be used for detecting a nucleic acid sequence and the detecting step is needed for quantification Thus, one of ordinary skill in the art at the time of the instant invention would have been motivated to apply the teachings of Hartley and Eberle et al. with a reasonable expectation of success to claim the instant invention because the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13) and the method of Eberle et al. provide a quick, simple more reliable and sensitive test (see column 2, lines 27-30). Thus, the rejection is maintained and restated in section 9.

3. The response argues that the amended language "measuring total nucleic acid in the sample". It is unclear whether or not the total nucleic acid is a specific nucleic acid or an unknown sequence.

4. Regarding the rejection of claims 4, 5, 13, 26, 27 and 33 under 35 U.S.C. 103(a) over Hartley in view of Wu et al. and Respess et al., the response argues that one of skill in the art would understand that a "binding species" is not the ligated nucleic acid itself, but a moiety

introduced into the product by attachment to one of the primers. Since the limitations in the claims involve using nucleic acid ligase, Wu et al. disclose a ligase amplification system used as an allele-specific detection with T4 DNA ligase (see pg. 561, first column, 2nd paragraph) and Respess discloses a method which involves an improved primer which is biotin labeled and has binding species since the amplified products hybridize to a bound probes (see column 12, lines 29-31). It indicates that there are binding species on the primer. Thus, there is no indication that the ligated nucleic acid itself has a "binding species". Therefore, the argument has not been found persuasive. Thus, the rejection is maintained and restated in section 10.

Specification

5. Claim 33 is objected to because of the following informalities: the word "then" in claims 13 and 33 might be misspelling . Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-40 are vague and indefinite because it is unclear how the total nucleic acid is measured via measuring the total amount of said at least one detectable species bound to said solid phase or measuring the total amount of said at least one detectable species or binding species.

b. Claims 8, and 29 are vague and indefinite because it is unclear whether or not the language "Klenow fragment (3'-5')" means that the polymerase has 3'-5' exonuclease activity. It is suggested to clarify uncertainty.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3, 6-12, 14-25, 28-32 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) in view of Eberle et al. (5,413,906).

Hartley discloses a random amplification method and kit using a random oligonucleotide primer in which the method uses at least one primer (see column 5, lines 10-24) (recited in instant claims 1-3, 11,14, 20, 23-25, 31), which may be substituted with biotin (see column 6, lines 39) which is detectable species; having promoter site for RNA polymerase which is binding species; attached to a solid phase through using a linker (see column 9, lines 35) (recited in instant claims 1-3, 6-7, 9, 11,14-16, 18, 23-25, 28, 30), and at least one dNTP used in the method (see column 10, lines 5). There are also capture probe to capture the amplified products on magnetic beads (see column 12, lines 13 and 40-43) (recited in instant claims 9, 18). The primer is 8 bases long preferred and other length such as 4-mer, 5-mer can be used (see column 6, lines 19-24) (recited in instant claims 1-3, 11,14, 20, 23-25, 31). The polymerase is Klenow fragment of DNA polymerase I (see column 4, lines 60) (recited in instant claims 1-3, 8, 17, 21, 23-25, 29). The reaction mixture contains pH 6.8, 400uM of the final concentration of dNTP, 5mM of magnesium and 10mM of 2-mercaptoethanol which is a reduce agent. The reaction contains at least one dNTP (see column 10, lines 1-8). The method might be desirable in the quantification of the amplification product (See column 6, lines 39-43).

The teachings of Hartley suggest instant claims 1-3, 6-12, 14-25, 28-32 and 34-37 in which a random primer at least 4 nucleotides in length and having detectable species or binding species is used, the mixture is contacted with a solid support and a kit is constructed. The

detectable species are as listed in instant claims 7, 15 and 28, the binding species are as listed in instant claims 6 and 16, the polymerases are as listed in instant claims 8, 17, 21 and 29, the solid supports are as listed in instant claims 9 and 18, and the dNTP is as listed in instant claims 10, 19 and 30, the condition of the method is listed in instant claim 12 and 32, and the length of the primer is listed in instant claims 11, 14, 20 and 31.

Hartley dose not disclose one dNTP which has binding species or detectable species, the concentration of magnesium between 0.05 mm and 500mM and the sum of the molarities is between 1mM and 500mM.

Eberle et al. disclose a method for determining polymerase activity in which a detectable mononucleoside triphosphate and immobilizable nucleoside triphosphate binding to a solid support are used (see column 2, lines 27-49, column 3, lines 50-68 and column 4, lines 1-21) (recited in instant claims 1-3 and 23-25). Eberle et al. also disclose that the method can be used to detect a promoter sequence (See column 10, lines 59 to column 11, lines 1-9). The promoter sequence is a nucleic acid sequence which indicates that the method of Eberle et al. will be used for detecting a nucleic acid sequence and the detecting step is needed for quantification

The teachings of Eberle et al. suggest one dNTP having at least one detectable species in instant claims 1-3 and 23-25. The detectable species is selected from the group consisting biotin in instant claims 7, 15 and 28.

One having ordinary skill in the art would have been motivated to combine the teachings of two references to modify the method of Hartley by using at least one nucleotide having at least

one binding species or detectable species as taught by Eberle et al. at the time of the instant invention was made with a reasonable expectation of success because the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13) and the method might be desirable in the quantification of the amplification product (See column 6, lines 39-43), and the method of Eberle et al. provide a quick, simple more reliable and sensitive test (see column 2, lines 27-30). Although Hartley and Eberle et al. do not disclose the concentration of magnesium between 0.05 mm and 500mM and the sum of the molarities is between 1mM and 500mM, one of ordinary skill in the art would have optimized the working condition by adjusting the concentration of the components used in the reaction with a reasonable expectation of success. This was well known practice in the art at time of the instant invention. One of ordinary skill in the art would have constructed the kit as taught by Hartley to include each element needed for conveniently practicing the method. This was also well known practice in the art at time of the instant invention. Thus, it would have been prima facie obvious to carry out the method as claimed.

10. Claims 4, 5, 13, 26, 27, 33 and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) in view of Wu et al. (Genomics, 1989, vol. 4, pg. 560-569) and Respess (5,599,662).

The teachings of Hartley are set forth in paragraph 9.

Hartley dose not disclose using a ligase and the labeled primer having binding species in the method.

Wu et al. disclose a ligase amplification system used as an allele-specific detection with T4 DNA ligase (see pg. 561, first column, 2nd paragraph) (as recited in claims 4, 5, 13, 26, 27, 33 and 39-40).

Respess discloses a method which involves an improved primer which is biotin labeled and has binding species since the amplified products hybridize to a bound probes. It indicates that there are binding species on the primer (see column 12, lines 29-31).

The teachings of Hartley, Wu et al. and Respess suggest the limitations of instant claims 4, 5, 13, 26, 27, 33 and 39-40 in which a random primer labeled and having binding species is used and a ligase is involved. The ligase is listed in instant claims 13 and 33.

One having ordinary skilled artisan in the art at the time of the instant invention would have been motivated to combine the teachings of three references to modify the method of Hartley by using ligase in the method as taught by Wu et al. and by using a primer having a binding species as taught by Respess at the time of the instant invention with a reasonable expectation of success because the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13) and the method might be desirable in the quantification of the amplification product (See column 6, lines 39-43), the improved primer of Respess also more specifically amplifies a target without the simultaneous

amplification of non-target sequences (see column 1, lines 58-67 and column 2, lines 1-4) and the method of Wu involves a ligase for allele- specific detection and is used in a detection system (See pg. 560, the Abstract). It would have been prima facies obvious to carry out the method as claimed.

11. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) in view of Kozlowski et al. (6,096,499).

The teachings of Hartley are set forth in paragraph 9.

Hartley dose not disclose using one nucleotide which has at least one second label.

Kozlowski et al. disclose an invention to modulate mammalian DNA primase activity (See column 3, lines 7) involving a DNA polymerase α for the further extension of the products of the DNA primase which can be useful to enhance the signal incorporation of labeled nucleotide (See column 5, line 44-52) using distinct label (See column 6, lines 42-55). There are a first labeled nucleotide having a first label incorporated in polynucleotide produced from template-directed polynucleotide synthesis and a second labeled nucleotide having a second label which can be distinguished from the first label of the nucleotide species (See column 6, lines 42-55).

The teachings of Hartley and Kozlowski et al. suggested the limitations of claim 38 in which a random primer at least 4 nucleotides in length and having first label is mixed, at least one nucleotide triphosphate having at least one second label, polymerase are added at a condition for polymerase chain reaction and then measure total nucleic acid in a sample. Although Kozlowski et al. do not disclose measuring a total nucleic acid in a sample in which a random primer with a

first label to label nucleotide is used, Hartley discloses using a random oligonucleotide primer in which the method uses at least one primer (see column 5, lines 10-24) (recited in instant claims 38), which may be substituted with biotin (see column 6, lines 39) which is detectable species. This suggests that a nucleotide sequence is labeled. Kozlowski et al. disclose using labeled nucleotide having distinct labels (See column 6, lines 42-55). A labeled ribonucleotide species has a first label and a deoxyribonucleotide species is labeled with a differentiable label, i.e. a differentiable label can be quantitatively distinguished from the first label by a conventional art-known technique (See column 7, lines 43-50).

One having ordinary skilled artisan in the art at the time of the instant invention would have been motivated to combine the teachings of two references to modify the method of Hartley by adding at least one nucleotide with a second label because the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13) with a biotin labeled primer (see column 6, lines 39) which would have been used by one having ordinary skill in the art for labeling a first label in a nucleotide sequence and the method might be desirable in the quantification of the amplification product (See column 6, lines 39-43) and the method of Kozlowski et al. involves using a differentially labeled nucleotide which will be quantitatively distinguished from the first label by a conventional art-known technique (See column 7, lines 43-50) and the method will be used for measuring the production of a nucleic acid

molecule (See column 29, lines 6-12). It would have been prima facies obvious to carry out the method as claimed.

12. Any inquiries concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (703) 305-7112. The examiner can normally be reached on Monday-Friday from 8:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr can be reached at (703) 308-2454.

Any inquiries of a general nature or relating to the status of this application should be directed to the Chemical/Matrix receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Art Unit 1656 via the PTO Fax Center located in Crystal Mall 1 using (703) 305-3014 or 308-4242. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Joyce Tung

February 25, 2001